REMARKS

Applicant acknowledges with appreciation the courtesy of the telephone interview extended the undersigned attorney by Dr. Kishore, the Examiner in charge of this application. Applicant wishes to emphasize that every effort is being made to overcome the rejections in the outstanding Official Action and to arrive at allowable subject matter. Applicant has rewritten the claims to more particularly define the invention taking into consideration the outstanding Official Action and believes that all the claims now present in the application are in full compliance with 35 U.S.C. 112 and are clearly patentable over the references of record.

In this regard, Applicant wishes to emphasize that the level of one of ordinary skill in the art to which the invention pertains must be taken into consideration. With respect to enablement, experimentation is permissible although undue experimentation is not. As stated on page 6, line 23 of Applicant's specification, as described below in the present invention, a similar immunological response can be obtained only by mixing the antigen with a lipid formulation which contains less complicated lipids having a substantially lower price and which can be formulated on a commercial basis is a very simple way. This is an economical aspect of the present invention.

The rejection of claims 92-141 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been carefully noted. This rejection is based upon Applicant's previous Amendment which introduces the term "emulsion" in the independent claims. While Applicant does not agree with the Examiner's contentions set forth in this Official Action, the claims have been amended and the term "emulsion" is no longer used in the new claim set and this rejection should be withdrawn.

The new claim set includes claims 142-193. These claims are fully supported by the specification as originally filed and as would be interpreted by one of ordinary skill in the art to which the invention pertains. All the previous claims canceled from the application have been canceled without prejudice or disclaimer.

Claim 142 substantially corresponds to previous claim 92. Besides the component i) monoglyceride and ii) fatty acid, water also composes part of the adjuvant, and has been included in the new claim and as fully supported by Applicant's specification. Furthermore, to specify the concentrations of monoglyceride and fatty acid in the adjuvant, Applicant has added the limitation "...wherein the concentration of i) is from 0.1 g to 50 g per 100 ml of water, and the concentration of ii) is from 1 g to 50 g per 100 ml of water." The basis for this amendment is found in Applicant's specification on p. 7, lines 17-20, as this passage would be interpreted by one of ordinary skill in the art to which the invention pertains. This is a claim limitation which cannot be ignored in evaluating the patentability of the claimed subject matter over the prior art and in compliance with 35 USC 112.

Claim 143 substantially corresponds to canceled claim 93. Claim 143 emphasizes a suitable composition of an adjuvant which further species the ratio between monoglyceride and fatty acid. Claim 143 reflects the fact that the total amount of lipids (amount of monoglyceride + amount of fatty acid) in a preferred embodiment of the invention is from at least 10 w/w % monoglyceride to 90 w/w % fatty acid and up to at the most 90 w/w % monoglyceride to 10 w/w % fatty acid. The basis for this amendment is found at p. 7, line 22. Again, these are claim limitations which cannot be ignored in evaluating the patentability of the claims now present in the application.

Furthermore, new claims 150, 164, 167, 172, 175, 189, 192 and 193 have been added to specific examples of monoglycerides i) and fatty acids ii). The basis for these new claims is found in Example 5 in the application, which describes adjuvants

comprising various monoglycerides (mono-olein (C18:1), lauryl-1-glycerate (C12) and capric-1-glycerate (C10)) and various fatty acids (oleic acid (C18:1), lauric acid (C12), capric acid (C10) and caprylic acid (C8)). Furthermore, Example 6 demonstrate that a combination of monoolein + caprylic acid works fairly well too, if administered s.c. primary followed by a nasal boost. 6 (page 10 line 12-page 11 line 4, and Example 7 describes that monooleate, monomyristate (C14), monolaurate and monocaprate together with caprylic acid is a suitable adjuvant for s.c. administration (page 11, line 7-page 12, line 4).

In addition, the antigen component is set forth in claim 159 which specifies the antigen component as selected from the group consisting of diphtheria toxin, influenza virus and rota virus. These are specific antigens as described in the specification and would be fully enabled as recognized by the Examiner in the Official Action.

The rejection of claims 92-141 under 35 U.S.C. 112, first paragraph, because while being enabling for the nasal administration of Diphtheria toxoid or influenza or rota virus antigens in micellar compositions containing monoolein and oleic acid, this does not provide reasonable enablement for generic monoglycerides and tarry acid of 6-24 carbon atoms. This rejection has been carefully considered but is most respectfully traversed. This is especially true when one takes into consideration the level of one of ordinary skill in the art to which the inventions pertains and bearing in mind that routine experimentation is permissible for one of ordinary skill in the art to find an enabling disclosure. Applicant most respectfully submits that based upon the detailed disclosure set forth in the present specification, the level of one of ordinary skill in the art and the relevant art at the time that the invention was made, one of ordinary skill in the art would find the specification enabling without undue experimentation. In addition, Applicant is entitled to broadly claim a broad invention to provide adequate protection for this important invention.

The Examples in the present application illustrates that a variety of monoglycerides and fatty acids (both saturated and unsaturated) may be use in an adjuvant according to the invention. Example 5 in the application describes adjuvants comprising various monoglycerides (monoolein (C18:1), lauryl-1-glycerate (C12) and capric-1-glycerate (C10)) and various fatty acids (oleic acid (C18:1, lauric acid (C12), capric acid (C10) and caprylic acid (C8)) besides and oleic acid (C18:1). Even though the combination of monoolein and oleic acid gives the highest IgG titer, other combinations (monoolein + caprylic acid and lauryl-1-glycerate + lauric acid) also give a good response (high IgG titer) when administered subcutaneous (s.c.). Furthermore, Example 6 and 7 demonstrate that a combination of monoolein, monomyristate (C14), monolaurate and monocaprate + caprylic acid works fairly well too, if administered s.c. primary followed by a nasal boost.

Furthermore, the Examiner doses not find the specification to provide reasonable enablement for generic antigens. The Examples describe two types of antigens that are used in all vaccines where adjuvants can be of use. One type is a purified protein, diphtheria toxoid, and the other type is killed microorganisms (influenza and rota virus). For the person skilled in the art and knowledgeable in vaccinology, these examples demonstrate that the adjuvant have a broad and general applicability. Accordingly, one of ordinary skill in the art would find the specification enabling without undue experimentation. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 92-141 under 35 U.S.C. 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been carefully considered but is most respectfully traversed in view of the amendments to the claims.

In the Official Action it is urged that the preamble in claim 92 and 93 recite "antigen" whereas the method part recites no antigen. Accordingly, in rewriting these claims, claims 142 and 143 more specifically reflect the fact that the immune response is enhanced to an antigen in a human or mammal exposed to said antigen. As the claims reads "...the method comprising...", i.e. it does not exclude other steps than the one mentioned, and is related to the aspect of administration of an adjuvant, not a vaccine, we do not find it necessary to include a further specific step of adding an antigen in the present claim 92 or 93. Please notice, that in claim 102 and 127 related to the administration of a vaccine, an antigenic component is specifically administered.

In response to the Examiner's arguments in respect of the phrase "immune responsive enhancing effective amount", Applicant would like to emphasize that the amounts specified in present claims 105 and 130 is to be interpreted as immune responsive enhancing amounts.

In response to the Examiner's arguments in respect of previous claims 104 and 128, and the amendment of claim 92 and 93, claims 104 and 128 has been deleted.

In response to the Examiner's arguments in respect of previous claims 105, 107, 129 and 131, the claims have been deleted. Accordingly, all of the rejections under 35 USC 112 have been obviated and these rejections should be withdrawn.

The rejection of claims 92-141 under 35 U.S.C. 103 as being unpatentable over WO 93/06921 by itself or in combination with Amselem, Wright, Koga, Carrano et al. individually or in combination has been carefully considered but is most respectfully traversed.

Applicant wishes to direct the Examiner's attention to the basic requirements of a prima facie case of obviousness as set forth in the MPEP § 2143. This section states that to establish a prima facie case of obviousness, three basic criteria first must be met. First, there must be some suggestion or motivation, either in the references themselves

or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Section 2143.03 states that all claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicant also most respectfully directs the Examiner's attention to MPEP § 2144.08 (page 2100-114) wherein it is stated that Office personnel should consider all rebuttal argument and evidence presented by applicant and the citation of In re Soni for error in not considering evidence presented in the specification.

It is stated at the top of page 7 of the Official Action that it would have been obvious to one of ordinary skill in the art to add oleic acid in the formulations of WO with the expectation of obtaining at least an additive effect or the best possible results since the references Amselem, Wright, Koga and Carrano each teach that oleic acid is used in vaccine preparations as an adjuvant. However, this represents no more than an obviousness to try standard which is not the standard of obviousness under 35 U.S.C. 103.

One of ordinary skill in the art would appreciate the teachings of WO which in the abstract notes that the particles, especially colloidal particles, comprising an interior

phase of a "non-lamellar reverse cubic, intermediate or hexagonal liquid crystal phase or a homogeneous L3 phase, and a surface phase of a lamellar crystalline or liquid crystalline phase, or an L3 phase does not suggest that of the present claim. That is, this disclosure teaches particles comprising monoglyceride, water and a so-called fragmentation agent.

As would be appreciated by one of ordinary skill in the art to which the invention pertains, the particles described in WO 93/06921 are prepared by mixing glycerol monooleate with water to obtain a cubic phase in the form of a solid gel. To this cubic phase is added a so-called "fragmentation agent" (p. 21, lines 26 - 29), the function of which is to break the gel into smaller particles which still maintains a cubic inner phase, and a surface phase, followed by sonication. In the Examples given in WO 93/06921 is described particles having an inner cubic phase comprising monoglyceride/poloxamer 407/water in the ratio 50/3.5/46.5 wt%, whereas the surface phase of the particles comprises monoglyceride/poloxamer 407/water in the ratio 6.5/4/89.5 wt % (p. 21, lines 15 - 20). A suitable so-called "fragmentation agent" according to the invention described in WO 93/06921 must be a substance, that facilitates the fragmentation of the monoglyceride/water gel into particles having an inner cubic phase.

As known by a person skilled in the art, a monoglyceride preparation may, depending on the purity, contain minor amounts of impurities in the form of diglycerides, triglycerides, glycerine and free fatty acids.

The monoglyceride preparation used in compositions as described in WO 93/06921 posses a high grade of purity and contains 98.8 % monoglyceride and a minor amount of impurities in the form of 1.0 % glycerol, 1.0 % diglycerides and 1.0 % free fatty acids (see page 20, line 29-30).

As the amount of the impurity fatty acid in the monoglyceride preparation does not exceed 1%, there will always be a ratio between monoglyceride to fatty acid in the

compositions described in WO 93/06921 of almost 100, i.e. there will always be 100 times more monoglyceride than fatty acid present in the compositions.

On the contrary, Applicant's adjuvant is prepared as follows: 1) monoglyceride and fatty acid are mixed to obtain a liquid mixture, 2) water is added followed by very briefly sonication to obtain a dispersion of monoglyceride/fatty acid particles in water, 3) pH is adjusted. Accordingly, Applicant's adjuvant does not at any point comprise a solid cubic phase and such teaching in the prior art does not provide the motivation to arrive at the present invention.

Accordingly, Applicant's adjuvant does not bear any resemblance with the composition described in WO 93/06921, and the fatty acid in Applicant's composition does not bear any functional resemblance with the "fragmentation agent" in WO 93/06921.

More specifically, the adjuvant according to Applicant contains a monoglyceride preparation comprising a minor amount (impurity) of fatty acid, and then an additional amount of free fatty acid together with water while the composition in WO 93/06921 only comprises a monoglyceride with a very small inherent amount (impurity) of free fatty acid. The amount of monoglyceride in Applicant's adjuvant may vary between 0.1 g to 50 g per 100 ml water, while the amount of free fatty acid may vary between 1 to 50 g per 100 ml water. In other words, the adjuvant claimed in the present invention comprises two distinct components and the total amount of free fatty acid exceeds the amount mentioned in WO 93/06921.

Moreover, the ratio of monoglyceride to fatty acid does not exceed 50, i.e. there may only be up to 50 times more monoglyceride than fatty acid in the adjuvant composition, as compared to the ratio of monoglyceride to fatty acid of 100 described in WO 93/06921. These are all claim limitations which cannot be ignored.

Furthermore, in a preferred embodiment (reflected by claim 143), the ratio of monoglyceride to fatty acid has to be at least 10 w/w % monoglyceride to 90 w/w % fatty acid and up to 90 w/w % monoglyceride to 10 w/w % fatty acid. Accordingly, in a preferred embodiment, there may only be 9 times more monoglyceride as fatty acid, as opposed to WO 93/06921. The lack of teaching of the invention in the primary reference is not overcome by the teachings of any of the references to Amselem, Wright, Koga, Carrano individually or in combination as set forth above, further in view of Isaacs cited before. None of these combinations renders the claims obvious and the necessary motivation to make the changes to the prior art is not found in the prior art but only in Applicant's specification. This represent impermissible hindsight.

In re Fritch, 23 USPQ 1780, 1784(Fed Cir. 1992) ("It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps.). Each of these combinations, has been carefully considered but is most respectfully traversed.

As noted above, WO 93/06921 describes compositions comprising monoglyceride, water and a "fragmentation agent". Examples of suitable fragmentation agents are e.g. poloxamer 407 (page 20, line 33) and poloxamer 188 (page 22, line 6). Monoglycerides are available in many grades of purity, starting from 80 % monoglyceride up to 100 %, and accordingly, in many monoglyceride preparations, impurities in form of triglycerides, diglycerides, glycerine and fatty acids are present. In the monoglyceride preparation used in WO 93/06921, having a high purity (98.8%) with respect to monoglyceride, there still are some impurities present in the form of 1.0 % glycerol, 1.0 % diglycerides and 1.0 % free fatty acids (page 20, lines 29-30).

The reason for using a monoglyceride having a very high purity, for the invention described in WO 93/06921, must most certainly be to avoid as many impurities in the preparation as possible, most likely in order to obtain the proper cubic phase.

Accordingly, why would a person skilled in the art want to increase the amount of any of these impurities? Clearly, there is no motivation in WO 93/06921 to lead a person skilled in the art to add an additional amount of any of the impurities glycerol, diglycerides or free fatty acids to the composition described in WO 93/06921. Furthermore, there is no indication to, that especially the addition of an additional amount of the free fatty acid impurity should be beneficial in any way, as opposed to the addition of glycerol or a diglyceride.

Furthermore, as explained above, the particles according to WO 93/06921 are prepared by a totally different process than Applicant's adjuvant, and comprise completely different phases.

Accordingly, Applicant submits that WO 93/06921 by itself does not comprise any motivation or incitement to lead a person skilled in the art to vary the amount of the impurity fatty acid in order to obtain an adjuvant composition used in a method according to the present invention.

As mentioned above, in order to obtain the particles in WO 93/06921, a "fragmentation agent" has to be added to the monoglyceride/water. The "fragmentation agent" is chosen from the synthetic agents poloxamer 407 (page 20, line 33) or poloxamer 188 (page 22, line 6). Another example of a suitable agent is DDAB (page 22, line 36). Further examples of "fragmentation agents" are given on page 19, lines 7-13 (e.g. glycoproteins, polysaccharides, xanthan, PVP and carboxymethylcellulose) Starting from WO 93/06921 a person skilled in the art might be motivated to search for other "fragmentation agents". However, there is no indication in WO 93/06921 that an alternative "fragmentation agent" may be found among any of the impurities of the monoglyceride used for the compositions in WO 93/06921. Furthermore, according to information from Ulf Schröder, founder and CSO of Eurocine, it is not possible to obtain an adjuvant composition as described in US 09/147,67 by adding oleic acid to the cubic

phase monoglyceride/water solid gel according to the method described in WO 93/06921.

The four publications described in details below all mentions the fatty acid oleic acid as one component out of many in a formulation. No monoglycerides are mentioned in any of the formulations in the four publications, i.e. there are no indications in any of the four prior references, that the oleic acid mentioned in these could be formulated together with monoglyceride, and there is no teaching in any of the references of an additive effect, or the use of oleic acid as a "fragmentation agent". Starting from WO 93/06921 and wanting to find alternative "fragmentation agents" for use in the compositions, none of the four references comprises any indications of that oleic acid would be a suitable choice.

Moreover, none of the references teach that the total fatty acid content should exceed 1% (w/w) in a suitable adjuvant, let alone specifically recited amounts or ratios.

Anselem describes vaccine compositions that are nanoemulsions of particles having a lipid core, which is surrounded by at least one phospholipid bilayer (emulsomes). The compositions described in Anselem comprise at least 5 different components besides fatty acids. The emulsomes further comprises a high content of phospholipids. In the description is mentioned that the lipid compositions suitable for use as the lipid core of the emulsomes may be triglycerides, ester of monounsaturated fatty acids, monoester of fatty acids, cholesterol and cholesterol esters and that the lipid cores may further comprise antioxidant. It is also mentioned that negatively charged lipid molecules such as oleic acid may be added to the lipid phase of the emulsomes to increase the zeta potential of the composition. The emulsomes does not comprise any monoglycerides.

Again, there is no indication in Anselem of fatty acids being an obvious choice to formulate together with monoglycerides in an adjuvant. When reading the teaching

of WO 93/06921 and Anselem, there are in our opinion no indications that would lead person skilled in the art to pick out the monoglyceride component of WO 93/06921 and the fatty acid component of Anselem and combine these. Starting from WO 93/06921 searching for an alternative fragmentation agent, Anselem contains no indication at all of, that oleic acid would be a suitable choice.

Wright teaches an oral preparation useful as a vaccine against gram-negative bacterial infection. The gist of the invention is the use of a lipid vesicle preparation comprising a masking agent, which disguises the fecal-like smell of the bacteria. The preparation comprises a number of different substances, such as glycerol monostearate, soya steroler, soybean oil, cherry or peppermint oil, polysorbate 60, oleic acid and water. The function of oleic oil in the composition is not described. In the Examples is mentioned a composition comprising 0.1 % oleic acid, i.e. a very small amount of oleic acid as compared to the amounts used in Applicant's adjuvant.

Oleic acid is only mentioned as one component among many, and its function in the composition is not described. Accordingly, starting from WO 93/06921 searching for an alternative "fragmentation agent", in our opinion there is no indication what so ever in the Wright application to lead a person skilled in the art to pick out especially oleic acid as an obvious choice for use together with a monoglyceride/water gel as a "fragmentation agent".

Furthermore, the concentration of oleic acid in the composition of Wright is only 0.1 % - which is much less than the amount used in the invention according to Eurocine, and even less than already present in the monoglyceride used for the composition in WO 93/06921. Applicant submits that one of ordinary skill in the art would see that the small amount of oleic acid used does most certainly not render it the first, obvious choice to combine with the teaching of WO 93/06921.

Koga describes a vaccine for dental caries. The main aspect of the patent is the preparation of a protein antigen from Streptococcus mutans. The patent describes a vaccine comprising a protein antigen formulated together with carriers, diluents or other additives. As one component among the vast number of additives mentioned is mentioned oleic acid as an adjuvant fat-soluble component. Furthermore glycerin (glycerol) is mentioned as a suitable humectant.

Again, Applicant finds that oleic acid is only mentioned as one component among many, and in Applicant's opinion there is no indication in the application that the specific component oleic acid are a suitable choice for use together with monoglyceride in an adjuvant composition. The only common feature between WO 93/06921 and Koga is that both documents mentioned that fatty acid may be present in an adjuvant (as an impurity in WO 93/06921 and as fat-soluble component in Koga). However, both documents also mention that glycerol may be present. Starting from WO 93/06921 searching for an alternative "fragmentation agent" Koga comprises no motivation at all to lead a person skilled in the art to choose oleic acid.

Carrano describes a method of introducing genetic material into a cell. The genetic material is distributed together with a genetic vaccine facilitater (GVF) agent that is selected from anionic lipids, enzymes, saponins etc. Oleic acid is mentioned as an example of a GVF.

The GVF consists of only one component. Furthermore, the genetic material/GVF is not intended for mucosal administration.

Oleic acid is mentioned as one example of an anionic lipid. Glycerol, one of the other impurities of the monoglyceride used in WO 93/06921 is also mentioned as an example of a suitable GVF agent (column 18, lines 38-47).

In Applicant's opinion it would not be obvious to combine the teaching of Carrano, that describes a one-component system for non-mucosal use for the administration of

genetic material wherein oleic acid/fatty acids and glycerol are mentioned as two examples of components out of a vast number of components with the teaching of WO 93/06921, since we do not find any references or indications for doing so. Moreover, there is no indication at all to why oleic acid should be chosen instead of e.g. the other impurity of monoglyceride, glycerol. A person skilled in the art searching for an alternative fragmentation agent for use in the compositions described in WO 93/06921 would find no motivation in Carrano to add oleic acid as a fragmentation agent.

All four references mentioned above taken together may have the mentioning of oleic acid in common. However, oleic acid has no common function in the four references, as e.g. a "fragmentation agent". Accordingly, even though oleic acid is mentioned in all four references, there is no motivation to why a person skilled in the art should chose oleic acid as an alternative to the "fragmentation agents" mentioned in WO 93/06921. Furthermore, as described above, the addition of oleic acid to the cubic phased monoglyceride/water solid gel would not lead to an adjuvant as described in US 09/147,367.

WO 93/06921 in combination with Amselem (US 5,716,637), Wright (5,730,989), Koga (5,352,450) and Carrano (5,739,118) individually or in combination, further in view of Isaacs.

Item 3. The examiner rejects claim 92-141 in view of WO, Amselem, Wright, Koga, Carrano and Isaacs. According to the Examiner Isaacs teaches the effectiveness of the combination of a monoglyceride and a fatty acid in killing viruses and bacteria. Furthermore, he believe that one skilled in the art would be motivated to add a fatty acid to the formulations of WO since fatty acids are also effective against viruses as taught by Isaacs.

Applicant believes that Isaacs is related to antiviral and antibacterial compositions consisting of fatty acids and monoglycerides. We find that the Isaac patent described

a totally different invention, since the Isaacs patent concerns a formulation for killing viruses and bacteria - not a method for enhancing an immune response by administering an adjuvant formulation together with an antigen. Therefore, the fact that fatty acids are also effective against viruses are not important at all for the preparation of an adjuvant composition. As we see it, it would not be obvious for a person skilled in the art to combine the teaching, since the technical fields are not related at all. Starting from WO 93/02691 searching for an alternative fragmentation agent for use in an adjuvant a person skilled in the art would not look to Isaacs as this patent is related to the field of compositions with antiviral and antibacterial effect, and not to methods for enhancing an immune response by the administration of adjuvants. Accordingly, it is most respectfully requested that this rejection be withdrawn.

In view of the above arguments and further amendments to the claims, applicant respectfully requests reconsideration and allowance of all of the claims which are currently pending in the application.

Respectfully submitted,

BACON & THOMAS, PLLC

By 
Richard E. Fichter
Reg. No. 26,382

625 Slaters Lane, Fourth Floor
Alexandria, Virginia 22314
Phone: (703) 683-0500
Facsimile: (703) 683-1080

REF/kdd
A08.wpd

Date: March 22, 2005